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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|-----------------|-------------|----------------------|---------------------|
| 09/320,156      | 05/26/99    | ROSENBLUM            | M D5425CIP2         |

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EXAMINER

CANELLA, K

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| 1642     | 11           |

DATE MAILED: 12/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.  
09/320,156

Applicant(s)  
Rosenblum et al

Examiner  
Karen Canella

Group Art Unit  
1642



☐ Responsive to communication(s) filed on \_\_\_\_\_

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claim

☒ Claim(s) 1-21 is/are pending in the applicat

Of the above, claim(s) 1-14, 20, and 21 is/are withdrawn from consideration

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 15-19 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

***Response to Arguments***

1. Claim 16 has been amended. Claims 15-19 are under consideration.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections Maintained***

3. The rejection of claim 18 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to make/use the invention, is maintained for reasons of record. Acknowledgment is made of applicants stated intention to fulfill the deposit requirements as recited on pg. 2 of Paper No. 10.

***New Claim Rejections***

4. Claims 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over . Claim 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bacus et al (USP 5,514,554, effective filing date 9/27/91) in view of Rosenblum et al (Cancer Communications, 1991) and Hudziak et al (Molecular and Cellular Biology, 1989). Claim 15 and 19 are drawn to a composition comprising a conjugate of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein, and pharmaceutical compositions thereof. Bacus et al teach ricin A conjugated via SPDP chemistry to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein, also known as Her-2 receptor. Rosenblum et al teach tumor necrosis factor conjugated via SPDP chemistry to an antibody which binds specifically to epitope A of gp240 antigen found on the surface of melanoma cell lines and fresh tumor samples. Rosenblum et al do not teach the conjugate of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. Hudziak et al teach an anti-p185<sup>HER2</sup> /anti-c-erbB-2 monoclonal antibody which increases the sensitivity of p185<sup>HER2</sup> expressing tumor cells to the cytotoxic effects of TNF.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to conjugate TNF via SPDP chemistry to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. Hudziak has demonstrated that cells expressing HER-2/c-erbB-2 showed increased resistance to the cytotoxic effects of TNF

and that this resistance can be overcome by the co-administration of an anti-proliferative antibody directed against the extracellular portion of the c-erbB-2 protein. Rosenblum discloses improved tumor-targeting of TNF to target cell lines by the use of an antibody which binds specifically to the extracellular portion of the target polypeptide conjugated tumor necrosis factor by SPDP conjugation.

One of ordinary skill in the art would have been motivated to conjugate TNF with an antibody directed against the extracellular epitope of c-erbB-2 protein with a reasonable expectation of success by the teachings of Bacus in view of Rosenblum and Hudziak. One of skill in the art would have been motivated to conjugate TNF with an antibody directed against the extracellular epitope of c-erbB-2 protein to attain an anti-proliferative and heightened cytotoxic effect as taught by Hudziak and an improvement in the tumor-targeted delivery of TNF as taught by Rosenblum. Rosenblum teaches that TNF retains activity after SPDP conjugation, therefore the chemical conjugation did not disrupt the domains of TNF essential to its function. Bacus et al teach that the anti-c-erbB-2 antibody conjugated to ricin A by means of SPDP chemistry retains its affinity to the c-erbB-2, thus the SPDP chemical conjugation to ricin A did not disrupt the binding site of the antibody or adversely affect the specific targeting of the SPDP formed conjugate.

5. Claims 15, 16, 17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wels et al (USP 5,571,894, effective filing date 7/15/91) in view of Hoogenboom et al (Biochimica et Biophysica Acta, 1991, Vol. 4, pp. 345-354 and Hudziak et al (Molecular and Cellular Biology, 1989). Claims 15, 16, 17 and 19 are drawn to a composition comprising a fusion of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein, and pharmaceutical compositions thereof, wherein said fusion protein is recombinantly produced. Wels et al teach a recombinant single chain antibody directed toward the extracellular portion of c-erbB-2 fused to a effector useful for therapeutic purposes such as toxins or other drugs (column 3, lines 12-37). Wels et al do not specifically teach TNF as an effector molecule fused to the anti- c-erbB-2 single chain antibody. Hoogenboom et al teach a


recombinant antibody-TNF fusion protein. Hudziak et al teach an anti-p185<sup>HER2</sup> /anti-c-erbB-2 monoclonal antibody which increases the sensitivity of p185<sup>HER2</sup> expressing tumor cells to the cytotoxic effects of TNF. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a recombinant fusion protein of TNF and the single chained anti-c-erbB-2 antibody. One of ordinary skill in the art would have been motivated to conjugate TNF to a single chained antibody directed against the extracellular epitope of c-erbB-2 protein with a reasonable expectation of success by the teachings of Wels in view of Hoogenboom and Hudziak. Hudziak teaches the combined administration of an antibody directed against an extracellular epitope of c-erbB-2 protein and TNF to attain an anti-proliferative and heightened cytotoxic effects. Wells et al teach the advantages of recombinantly expressed single chained antibody directed against an extracellular epitope of c-erbB-2 protein and fusion proteins thereof. Hoogenboom teaches the recombinant expression of general antibodies fused to TNF.

6. All other rejections and objections as recited in Paper No. 8 are withdrawn.

### *Conclusion*

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.  
Patent Examiner, Group 1642  
December 17, 2000

  
ANTHONY G. CAPUTA  
EXAMINER  
11600